PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P3179 WO ORD	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/004470	International filing date *(day/month/year)* 22.10.2004	Priority date *(day/month/year)* 23.10.2003
International Patent Classification (IPC) or national classification and IPC C08J3/205, C08J7/06, B01J3/00		
Applicant UNIVERSITY OF NOTTINGHAM et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.05.2005	03.01.2006
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004470

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-37	as originally filed
Claims, Numbers	
1-25	received on 25.05.2005 with letter of 20.05.2005
Drawings, Sheets	
1/3-3/3	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1,2,3,5,6,19,23,24
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3,19,20,22

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 3,19,20,22

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004470

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,2,4-18,21,23-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2,4-18,21,23-25
Industrial applicability (IA)	Yes:	Claims	1,2,4-18,21,23-25
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 20 May 2005 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

1. The subject-matter of claims 1, 2, 6, 23 and 24 appears to contain added matter as far as the feature "under supercritical plasticizing conditions" has been replaced by "under supercritical conditions". Applicants have not provided any evidence that said features are identical.

2. The subject-matter of claims 3, 19 and 20 because the forms of the compositions disclosed on page 32, lines 6 to 8, were not taken therein (see also item III below).

3. The subject-matter of claims 5, 6, 23 and 24 because page 8, lines 8 to 25 defines the temperatures therein disclosed as "plasticising temperatures" not general process temperatures and the range 30 to 55 °C is not disclosed therein. Note also that it is not clear (Article 6 PCT) what the expressions "temperature in the range 30 to 55 °C and less than or equal 140°C" and "temperature....less than the.. non-viscous state of the polymer substrate" may mean.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 3, 19, 20 and 22 of the application has not been searched (Article 17(2)(a)(ii) and (2)(b) PCT, and Rule 39.1(iv) PCT). Therefore, claims 3, 19, 20 and 22 need not be the subject of an international preliminary examination (Rule 66(1)(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 01/91729 A (BREITENBACH JOERG ; BASF AG (DE); HERR DIETER (DE); LAUX VOLKER (DE);) 6 December 2001 (2001-12-06)
D2: WO 01/37808 A (LIPOCINE INC) 31 May 2001 (2001-05-31)
D3: WO 02/090085 A (XU JINGYI ; CARDONA JUAN C (US); KIM ROLAND Y (US); NG JEFFREY L (US);) 14 November 2002 (2002-11-14)
D4: WO 02/47893 A (UNIV BRUNEL ; HORNSBY PETER RIDSDALE (GB); MATTHEWS SIOBHAN OLIVE (GB)) 20 June 2002 (2002-06-20)
D5: WO 95/24830 A (CORNELL RES FOUNDATION INC) 21 September 1995 (1995-09-21)
D6: WO 98/51347 A (UNIV NOTTINGHAM ; HOWDLE STEVEN MELVYN (GB)) 19 November 1998 (1998-11-19)
D7: WO 2004/024802 A (TOLLETT IAN ; MATTHEWS JOHN (IE); SCF PROC LTD (IE); MATTHEWS SIOBHAN) 25 March 2004 (2004-03-25)

The subject-matter of claims 1, 2, 4 to 18, 21 and 23 to 25 of the present application appears to be novelty anticipated (Article 33(2) PCT) by the shaped polymer composites or polymeric matrices containing active components, methods for their preparation involving sub- or supercritical fluids and apparatuses used in said methods as disclosed in documents D1 to D5 (see passages cited in the search report). Concerning the disclosure of document D6, applicants' attention is also drawn to the fact that a composition or composite material is not automatically novel when is prepared by a different process, this process must be shown to always and unequivocally provide the resulting composition or composite material with least a differing material feature from the known compositions or composites. Therefore, the composites prepared in D6 (see passages cited in the search report) also appear to anticipate the subject-matter of claims 24 to 25 of the application. Furthermore D7 (see passages cited in the search report) would also anticipate (Article 33(2) PCT) the claimed subject-matter because it does not appear to be fairly based on the priority documents GB20030024720 or GB20040003361. It is pointed out that no

novelty or inventive step may be based on added or unclear subject-matter. Furthermore, although claims 1, 2, 6, 23 and 24 have been drafted as separate independent claims, they appear to relate basically to the same subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

CLAIMS

1. Process for preparing active polymer extrudate comprising polymer matrix and guest matter, the process comprising contacting a polymer substrate and guest matter with a supercritical fluid under supercritical conditions of elevated temperature and/or pressure to plasticise the polymer substrate and incorporate guest matter and extruding polymer substrate incorporating guest matter under supercritical conditions via an extrusion orifice into a collection zone or a mould with simultaneous or subsequent release of pressure, whereby extrudate is obtained comprising a solid admixture of polymer matrix and guest matter in form conferred by the orifice or the mould wherein extrudate is in the form of tubes, cylinders, rods, ribbons, fibrils, filaments, fibroids or fibres.

2. Process for preparing active polymer extrudate comprising polymer matrix and guest matter, the process comprising contacting a polymer substrate and guest matter with a supercritical fluid under supercritical conditions of elevated temperature and/or pressure to plasticise the polymer substrate and incorporate guest matter and extruding polymer substrate incorporating guest matter under supercritical conditions via an extrusion orifice into a collection zone or a mould with simultaneous or subsequent release of pressure, whereby extrudate is obtained comprising a solid admixture of polymer matrix and guest matter in form conferred by the orifice or the mould wherein extrudate is in the form of sheets or films.

3. Process as claimed in Claim 1 or 2 for preparing extrudate suitable for topical, rectal, parenteral, mucosal, epicutaneous, subcutaneous, intravenous or intrarespiratory application route or as a structural implant in the human or animal body or in living matter.

4. Process according to any of Claims 1 to 3 conducted in the substantial absence of additional solvent.

5. Process according to any of Claims 1 to 4 conducted at temperature in the range 30°C to 55°C and less than or equal to 140°C.

6. Process for preparing active polymer extrudate comprising polymer matrix and guest matter, the process comprising contacting a polymer substrate and guest matter with a supercritical fluid under supercritical conditions of elevated temperature and/or pressure to plasticise the polymer substrate and incorporate guest matter and extruding polymer substrate incorporating guest matter under supercritical conditions via an extrusion orifice into a collection zone or a mould with simultaneous or subsequent release of pressure, whereby extrudate is obtained comprising a solid admixture of polymer matrix and guest matter in form conferred by the orifice or the mould in the form of tubes, cylinders, rods, ribbons, fibrils, filaments, fibroids or fibres characterised in that the process is conducted at temperature 30°C to 55°C and less than or equal to 140°C and less than the Tg, Tm or non-viscous state of the polymer substrate.

7. Process according to any of Claims 1 to 6 conducted with polymer substrate of molecular weight in the range 20 to 50 kDa or 50 to 200 kDa.

8. Process as claimed in any of Claims 1 to 7 wherein two or more polymer types are contacted with supercritical fluid as discrete components and co-extruded to form a composite extrudate having two or more polymer layers or zones.

9. Process as claimed in any of Claims 1 to 8 comprising plural guest entities comprising guest matter of one type for one intended function together with guest matter of another type for a same or different intended function, for example one or more drugs and one or more excipients.

10. Process according to any of Claims 1 to 9 conducted with orifice dimensions in the range 0.001-10 millimetre, preferably 0.001-2 millimetre and length in the range 0.1 millimetre to 1 metre.

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11. Process according to any of Claims 1 to 10 conducted with orifice of increasing dimension along its length, preferably increasing at a first angle with respect to the axis and optionally at a second angle in respect to the axis at the orifice outlet.

12. Process as claimed in any of claims 1 to 11 wherein an orifice is one of a plurality of orifices which may be independent or which may be adjacently or coaxially or concentrically aligned to form a plurality of simple extrudates or to form a composite extrudate as hereinbefore defined, and may additionally or alternatively comprise a solid core or the like, whereby hollow extrudate is obtained for example an annular orifice may provide tubes or cylinders.

13. Process according to any of Claims 1 to 12 wherein extrusion is into a collection zone at positive, ambient or negative pressure, which may be greater or less than the supercritical pressure and is preferably in the range 50 to 140 bar or in the range 1 to 50 bar.

14. Process according to any of Claims 1 to 13 wherein polymer substrate is selected from any amorphous, semi-crystalline or crystalline polymer, suitably polymers such as polyesters, poly (ortho esters), polyanhydrides, poly(amino acids), poly(pseudo amino acids), polyphosphazenes, azo polymers; vinyl polymers poly(acrylic acid), poly(methacrylic acid), polyacrylamides, polymethacrylamides, polyacrylates, Poly(ethylene glycol), Poly(dimethyl siloxane), Polyurethanes, epoxy, bis-maleimides, methacrylates such as methyl or glycidyl methacrylate, Polycarbonates, Polystyrene and derivatives; carbohydrates, polypeptides and proteins; and copolymers thereof.

15. Process according to any of Claims 1 to 14 wherein guest matter is selected from biofunctional or non-biofunctional material including but not limited to:

(1) (pharmaceutical) drugs and veterinary products;

(2) agrochemicals as pest and plant growth control agents;

(3) human and animal healthcare products;

(4) human and animal growth promoting, structural, or cosmetic products including products intended for growth or repair or modelling of the skeleton, organs, dental structure and the like;

(5) absorbent biofunctional materials for poisons, toxins and the like;

(6) functioning matter such as any nutrient dependent, biological matter which is characterised by replication, division, regeneration, growth, proliferation or the like;

(7) organic or inorganic materials for use in dyeing, constructing textiles, electronic materials and the like;

(8) SMART materials.

(9) formulating agents which stabilise or enhance the functional material.

16. Process as claimed in any of claims 1 to 15 wherein guest matter is present in an amount of $1x10^{-12}$ to $1x10^{-6}$ or $1x10^{-6}$ to 1 wt%, more preferably in low volumes in the range $1x10^{-12}$ to $1x10^{-9}$, $1x10^{-9}$ to $1x10^{-6}$ or 0.01 or 0.1 to 1 wt%.

17. Process as claimed in any of claims 1 to 15 wherein guest matter is present in an amount of 1.0 wt% up to 50 wt%.

18. Polymer extrudate comprising polymer matrix and guest matter as hereinbefore defined in any of Claims 1 to 23 as a solid admixture in extrudate form in the form of tubes, cylinders, rods, ribbons, fibrils, filaments, fibroids or fibres, wherein the polymer matrix comprises polymer of molecular weight in the range 20 to 50 kDa or 50 to 200 kDa.

19. Polymer extrudate as claimed in Claim 18 suitable for topical, rectal, parenteral, mucosal, epicutaneous, subcutaneous, intravenous or intrarespiratory application route or as a structural implant in the human or animal body or in living matter wherein guest matter is present in an amount of $1x10^{-12}$ to $1x10^{-6}$ or $1x10^{-6}$ to 1 wt%, more preferably in low volumes in the range $1x10^{-12}$ to $1x10^{-9}$, $1x10^{-9}$ to $1x10^{-6}$ or 0.01 or 0.1 to 1 wt%.

20. Polymer extrudate as claimed in Claim 18 suitable for topical, rectal, parenteral, mucosal, epicutaneous, subcutaneous, intravenous or intrarespiratory application route or as a structural implant in the human or animal body or in living matter wherein guest matter is present in an amount of 1.0 wt% up to 50 wt%.

21. Apparatus for use in the preparation of polymer extrudate using the process as hereinbefore defined in any of Claims 1 to 17 comprising a pressure vessel adapted for temperature and pressure elevation which may comprise means for mixing the contents, and wherein the pressure vessel includes means for extruding contents via an orifice as hereinbefore defined into a second collection vessel at lower pressure.

22. Extrudate as claimed in any of Claims 18 to 20 or a composition thereof or a product of the process as claimed in any of Claims 1 to 17 for use as a controlled release device such as a drug delivery device; in Pharmaceutical or Veterinary applications for example as a human or animal health or growth promoting structural or cosmetic product, natural or artificial implant, drug delivery or DNA delivery device; as an anti-microbial for example having bacteria -static or -cidal activity; as a natural or synthetic barrier capable of immobilising e.g. naturally occurring or artificially introduced poisons or toxins by e.g. absorption, interaction or reaction; in Agrochemical or crop protection applications; in the processing of thermally labile fibres for use in dying, textiles, electronics etc below the polymer Tg, Tm or melt viscosity; in incorporation of dyes and other thermally labile materials into polymers that cannot be formed by traditional processes e.g. melt extrusion and the like; or in incorporation of surfactants into fibres to control polymer properties.

23. Process for preparing polymer extrudate comprising contacting a polymer substrate with a supercritical fluid under supercritical conditions of elevated temperature and/or pressure to plasticise the polymer substrate and extruding polymer substrate under supercritical conditions via an extrusion orifice into a collection zone or a mould with simultaneous or subsequent release of pressure, whereby extrudate is obtained in form conferred by the orifice or the mould in the

form of tubes, cylinders, rods, ribbons, fibrils, filaments, fibroids or fibres characterised in that the process is conducted at temperature of 30°C to 55°C and less than or equal to 140°C.

24. Process for preparing polymer extrudate comprising contacting a polymer substrate with a supercritical fluid under supercritical conditions of elevated temperature and/or pressure to plasticise the polymer substrate and extruding polymer substrate under supercritical conditions via an extrusion orifice into a collection zone or a mould with simultaneous or subsequent release of pressure, whereby extrudate is obtained in form conferred by the orifice or the mould in the form of sheets or films characterised in that the process is conducted at temperature of 30°C to 55°C and less than or equal to 140°C.

25. Process as claimed in Claim 23 or 24 wherein polymer substrate comprises a thermally labile polymer, for example, poly(acrylonitrile) and copolymers thereof.